220. *The Constitution of Aspidospermine. Part II.* Ultraviolet Absorption of the* Bz-*Methoxy-tetra- and -hexa-hydrocarbazoles.*

By J. R. Chalmers, H. T. Openshaw, and G. F. Smith.

The 5-, 6-, 7-, and 8-methoxy-derivatives of tetrahydrocarbazole, hexahydrocarbazole, and 9-acetylhexahydrocarbazole have been prepared and their ultraviolet absorption spectra measured. Comparison with the spectra of aspidospermine and deacetylaspidospermine confirms that the alkaloid is a 7-methoxyindoline derivative.

Aspidospermine, $C_{22}H_{30}O_2N_2$, an alkaloid occurring in *Aspidosperma quebracho blanco* and *Vallesia glabra*, contains an acetamido-group, N(*a*)Ac, and a tertiary, basic nitrogen atom, N(*b*).[1] By distillation with zinc dust Witkop [2] obtained 3 : 5-diethylpyridine and an indole fraction (probably a mixture of 3-ethyl- and 3-methyl-indole). A study of the ultraviolet absorption spectra and colour reactions of aspidospermine and deacetylaspidospermine indicated that these bases are dihydroindoles rather than indoles,[2,3,4] and also showed that the acetylated nitrogen is directly attached to the aromatic ring. Aspidospermine also contains an aromatically bound methoxyl group, since hot hydriodic acid brings about deacetylation and demethylation and yields a phenolic base, aspidosine.[1]

Warnat [5] established the orientation of the methoxyl group in the dihydroindole alkaloids α- and β-colubrine by oxidation to the corresponding methoxy-*N*-oxalylanthranilic acids, but we have been unsuccessful in applying this method to aspidospermine. We therefore undertook the preparation of the four isomeric hexahydro-*Bz*-methoxycarbazoles and their *N*-acetyl derivatives, and the comparison of their absorption spectra with those of aspidospermine and deacetylaspidospermine.

When this work was undertaken, the only tetrahydro-*Bz*-methoxycarbazole known was the 6-isomer.[6] 1 : 2 : 3 : 4-Tetrahydro-8-methoxycarbazole was prepared by the action of hot glacial acetic acid on *cyclo*hexanone *o*-methoxyphenylhydrazone. Similar treatment of *cyclo*hexanone *m*-methoxyphenylhydrazone gave a mixture, separable by crystallisation and picrate formation, of the 5- and the 7-methoxy-isomer; the preponderant isomer was shown to be the 7-methoxy-compound by the resemblance of its absorption spectrum to that of tetrahydroharmine [7] and through the degradation of the derived *N*-acetylhexahydromethoxycarbazole described below. Recently, Cummins and Tomlinson [8] have prepared 1 : 2 : 3 : 4-tetrahydro-5-methoxycarbazole by an unequivocal method, and have also described an independent synthesis of the 7-methoxy-isomer, and their results confirm our assignment of structure. The ultraviolet absorption spectra of the isomeric tetrahydromethoxycarbazoles, shown in Fig. 1, are sufficiently different to afford a means of determining the position of a methoxyl group in a methoxyindole alkaloid of unknown structure; this method has been applied, for example, to reserpine [7] and ibogaine.[9]

Reduction of the tetra- to the hexa-hydrocarbazoles was achieved electrolytically or by means of tin and hydrochloric acid. The products are assumed to be the *cis*-isomers.[10] The absorption spectra of the hexahydromethoxycarbazoles and their *N*-acetyl derivatives

* Part I, Openshaw and Smith, *Experientia*, 1948, **4**, 428.

[1] Ewins, *J.*, 1914, **105**, 2738.
[2] Witkop, *J. Amer. Chem. Soc.*, 1948, **70**, 3712.
[3] Raymond-Hamet, *Compt. rend.*, 1948, **226**, 2154.
[4] Openshaw and Smith, *Experientia*, 1948, **4**, 428.
[5] Warnat, *Helv. Chim. Acta*, 1931, **14**, 997.
[6] Borsche, Witte, and Bothe, *Annalen*, 1908, **359**, 49.
[7] Dorfman, Furlenmeier, Huebner, Lucas, MacPhillamy, Mueller, Schlittler, Schwyzer, and St. Andre, *Helv. Chim. Acta*, 1954, **37**, 59.
[8] Cummins and Tomlinson, *J.*, 1955, 3475.
[9] Schlittler, Burckhardt, and Gellert, *Helv. Chim. Acta*, 1953, **36**, 1337.
[10] Gurney, Perkin, and Plant, *J.*, 1927, 2676.

FIG. 1.

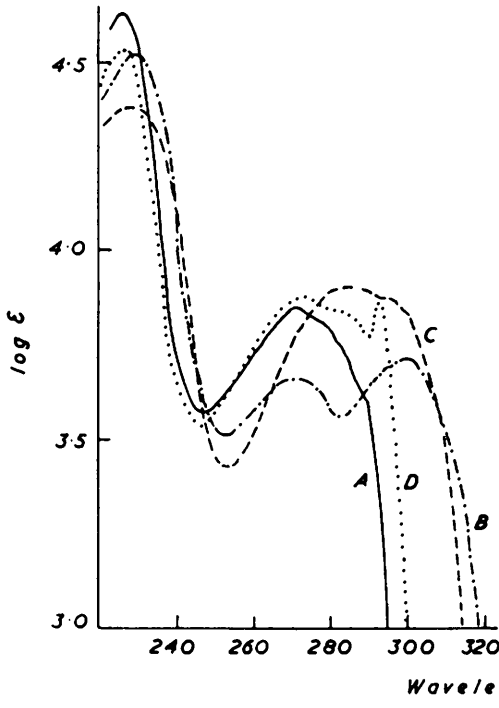
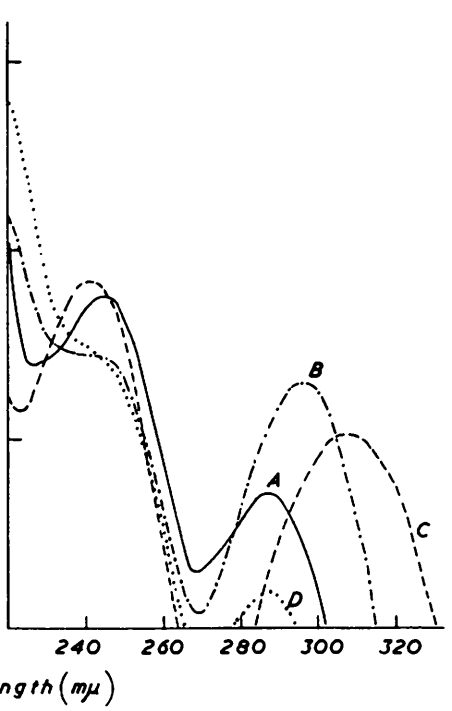


FIG. 2.



Wavelength (mμ)

FIG. 3.

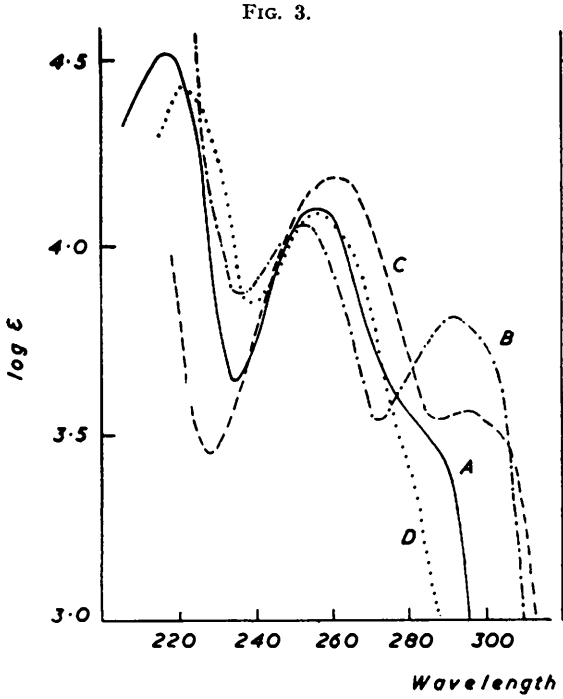
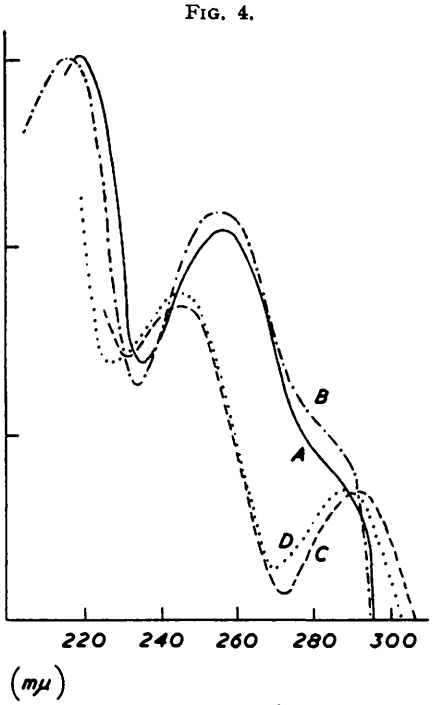


FIG. 4.

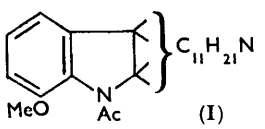


Wavelength (mμ)

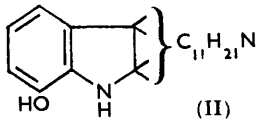
FIG. 1. *Absorption spectra of (A) tetrahydro-8-, (B) -7-, (C) -6-, and (D) -5-methoxycarbazole.*
FIG. 2. *Absorption spectra of (A) hexahydro-8-, (B) -7-, (C) -6-, and (D) -5-methoxycarbazole.*
FIG. 3. *Absorption spectra of (A) 9-acetylhexahydro-8-, (B) -7-, (C) -6-, and (D) -5-methoxycarbazole.*
FIG. 4. *Absorption spectra of (A) aspidospermine, (B) 9-acetylhexahydro-8-methoxycarbazole. (C) deacetylaspidospermine, and (D) hexahydro-8-methoxycarbazole.*

are shown in Figs. 2 and 3. The spectra shown in Fig. 2 show a close correlation with those recorded by Millson and Robinson [11] in their independent but parallel work with the hexahydro-*Bz*-methoxy-9 : 11-dimethylcarbazoles.

A comparison of the ultraviolet spectra of aspidospermine and deacetylaspidospermine with the synthetic 8-methoxy-compound is shown in Fig. 4 and leads to the assignment of the partial structure (I) to aspidospermine. This conclusion has also been reached by Witkop and Patrick [12] through a study of the properties of aspidosine (II), which behaves as an *o*-aminophenol derivative.

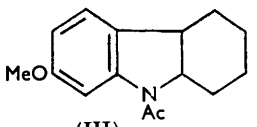


(I)

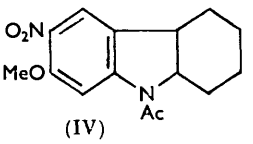


(II)

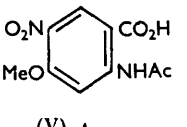
In order to confirm the orientation assigned to hexahydro-7-methoxycarbazole, it was converted into a derivative of 4-methoxyanthranilic acid. Preliminary experiments with the more plentiful 6-methoxy-isomer indicated that oxidation with permanganate caused breakdown of the aromatic nucleus; the principal product isolated was adipic acid. In order to increase the resistance of the aromatic ring to oxidation, 9-acetylhexahydro-7-methoxycarbazole (III) was nitrated, and the resulting mononitro-compound (probably IV) was oxidised. Besides adipic acid (5%), a small yield (2%) was obtained of an acid which did not depress the melting point of the nitration product (probably V) of 2-acetamido-4-methoxybenzoic acid (VI).



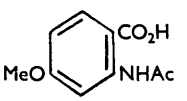
(III)



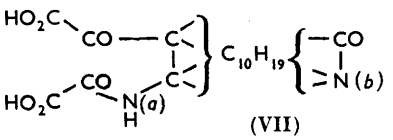
(IV)



(V)



(VI)



(VII)

In an attempt to apply a similar procedure to aspidospermine, the alkaloid was found to be smoothly nitrated to nitroaspidospermine, which on hydrolysis gave deacetylnitroaspidospermine. Oxidation of nitroaspidospermine with barium permanganate gave no methoxynitroanthranilic acid derivative, however; much barium nitrate was formed, indicating extensive breakdown of the aromatic ring. The only other crystalline product was an acid, probably $C_{17}H_{22}O_7N_2$, which may have the structure (VII).

Experimental

Absorption spectra were measured in EtOH.

1 : 2 : 3 : 4-*Tetrahydro*-5- *and*-7-*methoxycarbazoles*.—*m*-Methoxyphenylhydrazine [13] (20·15 g.) and *cyclo*hexanone (14·6 g.) were mixed, reaction being exothermic and water separating. Acetic acid (100 ml.) was added, and the mixture was heated to 95°; it was then removed from the steam-bath until the vigorous reaction, which caused the mixture to boil, had slackened; the mixture was then boiled for 10 min., and allowed to cool. The mixed tetrahydrocarbazoles (22·3 g., 75%), m. p. 102—106°, crystallised. A further quantity was obtained by distilling the

[11] Millson and Robinson, *J.*, 1955, 3362.
[12] Witkop and Patrick, *J. Amer. Chem. Soc.*, 1954, **76**, 5603.
[13] Kermack, Perkin, and Robinson, *J.*, 1921, **119**, 1602.

mother-liquor under reduced pressure; after acetic acid and acetamide had been removed, the tetrahydrocarbazoles (4·68 g.) distilled at 220—230°/15 mm., and crystallisation from methanol gave colourless crystals (2·35 g.), m. p. 103—105°.

Crystallisation of the mixture (12 g.) from benzene (25 ml.) gave colourless leaflets (6·3 g.) of 1 : 2 : 3 : 4-tetrahydro-7-methoxycarbazole, m. p. 145—146°. After crystallisation from ethanol and vacuum-sublimation it had m. p. 148°, $\lambda_{max.}$ 229, 270, 300 mμ (ε 33,000, 4500, 5100 respectively) (Cummins and Tomlinson [8] give m. p. 148—149°) (Found : C, 77·6; H, 7·3; N, 7·0. Calc. for $C_{13}H_{15}ON$: C, 77·6; H, 7·5; N, 7·0%). The *picrate*, brown laths from methanol, had m. p. 137° (Found : N, 12·7. $C_{13}H_{15}ON,C_6H_3O_7N_3$ requires N, 13·0%). The benzene mother-liquor was concentrated and treated with alcoholic picric acid; the black, sparingly-soluble *picrate* of 1 : 2 : 3 : 4-tetrahydro-5-methoxycarbazole (2·4 g.), m. p. 170°, separated; a sample was recrystallised from ethanol without raising the m. p. (Found : C, 52·9; H, 4·1; N, 13·0. $C_{13}H_{15}ON,C_6H_3O_7N_3$ requires C, 53·0; H, 4·2; N, 13·0%). The base recovered from this picrate and crystallised from ethanol had m. p. 129—130°, raised by sublimation in a vacuum to 130—131°, $\lambda_{max.}$ 227, 273, 293 mμ (ε 35,000, 7600, 7400 respectively) (Cummins and Tomlinson [8] give m. p. 126—127°) (Found : C, 77·6; H, 7·4%).

1 : 2 : 3 : 4-*Tetrahydro*-8-*methoxycarbazole*.—A solution of the syrupy *cyclo*hexanone *o*-methoxyphenylhydrazone [from *cyclo*hexanone (3·5 g.) and *o*-methoxyphenylhydrazine (4·5 g.)] in glacial acetic acid (25 ml.) was cautiously heated to boiling; an exothermic reaction occurred with considerable darkening. The bulk of the acetic acid was distilled off at atmospheric pressure, and the residue was fractionated under reduced pressure; the fraction boiling at 190—205°/15 mm. (3·96 g.) was treated with picric acid (4·5 g.) in ethanol, and the resulting picrate was collected in two crops, (i) m. p. 141—144° (decomp.) (4·0 g.) and (ii) m. p. 139—142° (decomp.) (2·2 g.). Recrystallisation from ethanol gave 1 : 2 : 3 : 4-*tetrahydro*-8-*methoxycarbazole picrate* as purplish-black needles, m. p. 145—146° (decomp.) (Found : C, 53·4; H, 4·2; N, 12·8. $C_{13}H_{15}ON,C_6H_3O_7N_3$ requires C, 53·0; H, 4·2; N, 13·0%). The base recovered from this picrate was a syrup, b. p. 124°/0·08 mm., $\lambda_{max.}$ 226, 271 mμ (ε 42,000, 7050 respectively).

Hexahydromethoxycarbazoles.—(i) The tetrahydrocarbazole, dissolved in 50% sulphuric acid, was reduced electrolytically [14] at 25°, with lead electrodes and a current density of 0·03 amp./cm.^{2}. Reduction was considered complete when a sample of the catholyte remained clear on dilution with water. The diluted solution was extracted with ether to remove any unchanged tetrahydrocarbazole, after which it was made alkaline with ammonia, and the hexahydrocarbazole was isolated by means of ether. (ii) A mixture of the tetrahydrocarbazole (2 g.), tin (4 g.), ethanol (4 ml.), and concentrated hydrochloric acid (4 ml.) was heated on the steam-bath under reflux for several hours. The solution was decanted from undissolved tin, basified with concentrated aqueous sodium hydroxide, and extracted with ether. The ethereal solution was extracted with N-hydrochloric acid, the extract was basified, and the liberated hexahydrocarbazole was isolated by ether-extraction.

1 : 2 : 3 : 4 : 10 : 11-*Hexahydro*-5-*methoxycarbazole* distilled at 90° (bath-temp.)/0·005 mm. and formed colourless crystals, m. p. 53—55°, $\lambda_{max.}$ 240 (infl.), 288 mμ (ε 5600, 1270), from light petroleum (b. p. 40—60°) (Found : C, 76·4; H, 8·1; N, 7·2. $C_{13}H_{17}ON$ requires C, 76·8; H, 8·4; N, 6·9%). The *acetyl derivative*, prepared by treatment with acetic anhydride at 100° and purified by removal of unchanged basic material and distillation in a high vacuum, was a colourless gum, $\lambda_{max.}$ 222, 256 mμ (ε 26,000, 12,200) (Found : C, 72·9; H, 7·8; N, 5·7. $C_{15}H_{19}O_2N$ requires C, 73·4; H, 7·8; N, 5·7%).

1 : 2 : 3 : 4 : 10 : 11-*Hexahydro*-6-*methoxycarbazole*, b. p. 172°/9 mm., $\lambda_{max.}$ 242, 307 mμ (ε 8300, 3200), gave a *picrate*, m. p. 153—154° (Found : C, 53·1; H, 4·9; N, 13·0. $C_{13}H_{17}ON,C_6H_3O_7N_3$ requires C, 52·7; H, 4·6; N, 13·0%), and a *hydrogen oxalate* (from alcohol), m. p. 166—167° (decomp.) (Found : C, 61·1; H, 6·7; N, 4·6. $C_{13}H_{17}ON,C_2H_2O_4$ requires C, 61·4; H, 6·5; N, 4·8%). The *acetyl derivative* formed colourless prisms (from ethanol), m. p. 98—99°, $\lambda_{max.}$ 261, 295 mμ (ε 15,500, 3680) (Found : C, 73·3; H, 7·4; N, 6·0%).

1 : 2 : 3 : 4 : 10 : 11-*Hexahydro*-7-*methoxycarbazole* distilled at 124°/0·1 mm. and crystallised; its m. p. 30—33° was raised by repeated crystallisation from light petroleum to 37—38°; $\lambda_{max.}$ were 240 (infl.), 297 mμ (ε 5300, 4400) (Found : C, 76·9; H, 8·2; N, 6·7%). It formed a *hydrogen oxalate* (from ethanol), m. p. 183° (Found : C, 61·8; H, 6·4; N, 4·8%), and a rather soluble *picrate* (from methanol), m. p. 139—140° (decomp.) (Found : C, 52·7; H, 4·6; N,

[14] Perkin and Plant, *J.*, 1924, **125**, 1503.

13·1%). The *acetyl derivative* was a colourless syrup, b. p. 150° (bath-temp.)/0·001 mm., $\lambda_{max.}$ 252, 291 mμ (ε 11,500, 6500) (Found : C, 73·2; H, 7·7; N, 5·4%).

1 : 2 : 3 : 4 : 10 : 11-Hexahydro-8-methoxycarbazole, b. p. 94—96°/0·01 mm., crystallised in the refrigerator, and a sample pressed on porous tile had m. p. 29°. After purification through the hydriodide and distillation, the base melted sharply at 31° and had $\lambda_{max.}$ 245, 288 mμ (ε 7600, 2300). The *hydriodide*, precipitated by the addition of aqueous potassium iodide to a solution of the base in dilute acetic acid, formed prisms, m. p. 210—211°, from water, and needles, m. p. 211—212° from ethanol–ether (Found : C, 47·2; H, 5·5; N, 4·2. $C_{13}H_{17}ON,HI$ requires C, 47·1; H, 5·5; N, 4·2%). The picrate forms stout yellow prisms, m. p. 152—153° (decomp.), from methanol (Found : N, 13·0%). The *acetyl derivative* was a colourless gum, b. p. 140—150° (bath-temp.)/0·001 mm., $\lambda_{max.}$ 217·5, 256 mμ (ε 32,300, 12,600) (Found : C, 73·2; H, 7·9; N, 5·8%).

Degradation of 9-*Acetyl*-1 : 2 : 3 : 4 : 10 : 11-*hexahydro*-7-*methoxycarbazole*.—A solution of the acetyl compound (1·35 g.) in acetic acid (5 ml.) was slowly added to a mixture of nitric acid (21 ml.; *d* 1·42), acetic acid (5 ml.), and acetic anhydride (5 ml.) at −5°. After 1 hr. at −5° to 0°, the mixture was poured on ice and made alkaline with aqueous ammonia. The brown, amorphous product (1·6 g.) was suspended in water (200 ml.) at 70°, and 2% aqueous potassium permanganate (36 equivs.) was added with stirring during 2 hr., the temperature being gradually raised to 100°. After a further hour, the manganese dioxide was removed; after ignition it weighed 3·6 g., corresponding to the utilisation of 16·5 atomic proportions of oxygen. The filtered solution was acidified and the excess of permanganate was reduced with sulphur dioxide. The liquor was extracted with ether (2 × 150 ml.), and the material extracted was separated into acidic and non-acidic fractions. The former, a partly crystalline paste (167 mg.), was triturated with ether, and the undissolved pale yellow solid (32 mg.), m. p. 220—223° with previous sintering, was purified by sublimation in a vacuum followed by crystallisation twice from aqueous acetone; it then had m. p. 229—233°, undepressed by admixture with material, m. p. 229—234°, obtained by nitration of 2-acetamido-4-methoxybenzoic acid with nitric acid in acetic anhydride at 0°.

Concentration of the aqueous liquor to a small volume, followed by extraction with ether, gave an acidic fraction from which a small amount of adipic acid, m. p. and mixed m. p. 145—148°, was isolated.

Nitroaspidospermine.—Nitric acid (2 ml.; *d* 1·42; free from nitrous acid) was added with shaking to a solution of aspidospermine (1·01 g.) in glacial acetic acid (2 ml.) containing urea (50 mg.) at 40—45° during 10 min. After being heated at 45—50° for 30 min., the red mixture was poured on ice, basified with concentrated aqueous ammonia, and well extracted with ether. The ether-extracted material crystallised from methanol in two crops, both of m. p. 147—148° (0·943 g., 83%); the mother-liquor yielded an intractable red resin. Pure *nitroaspidospermine* separates from ethanol as pale yellow prisms, m. p. 149—149·5° (Found : C, 66·3; H, 7·3; N, 11·1; Ac, 10·1. $C_{22}H_{29}O_4N_3$ requires C, 66·1; H, 7·2; N, 10·5; Ac, 10·8%). This compound is recovered unchanged after 3 minutes' refluxing in acetic anhydride containing a trace of sulphuric acid.

Deacetylnitroaspidospermine.—Nitroaspidospermine (0·127 g.) was refluxed in 20% aqueous toluene-*p*-sulphonic acid for 2 hr. and the deep orange-red solution was worked up for basic material. This was obtained as an orange solid which crystallised from aqueous methanol in two crops, m. p. 144—146° (99 mg.) and m. p. 143—145° (5 mg.) (yield 91%). Pure *deacetylnitroaspidospermine* separates from aqueous methanol as deep yellow, pointed blades, m. p. 144—146° (Found : C, 66·7; H, 7·3; N, 11·8. $C_{20}H_{27}O_3N_3$ requires C, 67·2; H, 7·5; N, 11·7%).

Permanganate Oxidation of Nitroaspidospermine.—A well-stirred solution of pure nitroaspidospermine (1·11 g.) in stabilised acetone (50 ml.) was gradually treated with aqueous 0·7% barium permanganate (10 equivs.) at room temperature; the oxidising agent was used up 1 hr. after completion of the addition. Distilled water was added (100 ml.), and most of the acetone was boiled off on a boiling-water bath. Addition of barium permanganate was then continued at 100° until the solution remained pink after 1½ hr. at 100°. Altogether 39 atomic proportions of oxygen were used up.

The reaction mixture was filtered hot, the manganese dioxide was digested twice with 50 ml. of boiling distilled water for 1 hr., and the combined filtrates were treated with a little methanol to reduce the last traces of permanganate and then concentrated to small bulk *in vacuo*. A

small quantity of manganese dioxide was filtered off, and the yellow solution (30 ml.) was basified with barium hydroxide solution and extracted thrice with ether; the neutral and basic material thus obtained weighed 1·5 mg.

The aqueous layer was rendered acid to Congo-red with dilute sulphuric acid and extracted with ether (5 × 50 ml.); the combined extracts yielded a brownish-yellow resin (169 mg.) which partially crystallised under a little methanol as needles. After a few hours, this crystalline solid (23 mg.) was collected as an off-white material, sintering at 140° and becoming glassy at 152—160°. The mother-liquor failed to yield further crystalline material. The crystalline acid was recrystallised from methanol–acetone, very small colourless needles (14 mg.) being obtained (m. p. 159·5—161° without flowing); a further crystallisation changed the m. p. behaviour to a marked sintering from 150°, the substance clearing, but not flowing, at 160° (Found: C, 55·6; H, 5·9; N, 7·9. $C_{17}H_{22}O_7N_2$ requires C, 55·7; H, 6·0; N, 7·6%).

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